UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,972	12/04/2001	Kenneth W. Dobie	RTS-0335	2850

7590 12/22/2003

Jane Massey Licata
Licata & Tyrrell, P.C.
66 East Main Street
Marlton, NJ 08053

EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,972	DOBIE, KENNETH W.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) *15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10/16/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

12/04/01

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-2, 4-14, and 19-20 in Paper filed 10-02-03 is acknowledged. The traversal is on the ground(s) that examination of all of the claims together would not present an undue burden upon the examiner. This is not found persuasive because as per MPEP § 803, "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP§808.02." As stated in the initial restriction requirement, the claims of group I are classifiable in 536/23.1, 536/24.3 and 536/24.5, however the claims of group II are classifiable in 514/44, 435/375, and 435/6. Therefore, the examiner has shown by separate classification of groups I and II, evidence of sufficient burden on the examiner to search and examine invention groups I and II.

2. Claims 15-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Paper filed 10-02-03.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-2, 4-14 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmer and Sims (WO 97/37225 and WO 99/1935), Sims et al. (WO 99/36536), in view of Wiedmer et al. (2000), Branch (1998) Monia et al. and Agrawal et al.

5. Disclosed in the PCT publications WO 97/37225 and WO 99/19352 are a preparation of a phospholipid scramblase, a recombinant DNA sequence encoding a phospholipid scramblase protein and expression vectors used to express the protein (see for example page 15 of WO 97/37225). Also disclosed are inhibitors of phospholipid scramblase including monoclonal antibodies, and generally disclosed are antisense nucleotides derived from a DNA sequence encoding a phospholipid scramblase (see page 20 of 97/37225), as well as peptides and peptidomimetics. Further disclosed are methods to treat various diseases and/or conditions using said inhibitors, methods to quantitate the amount of phospholipid scramblase present, cells genetically engineered not to express phospholipid scramblase and those wherein the phospholipid scramblase promoter is altered to increase or decrease the expression of the gene (Wiedmer and Sims, 1999; Wiedmer and Sims, 1997).

Disclosed in the PCT publication WO 99/36536 are methods to extend the viability of mammalian cells by inhibiting the expression of a phospholipid scramblase, wherein the inhibition is via a phospholipid scramblase antisense RNA molecule, a mutant or truncated form of a phospholipid scramblase such as an alternatively spliced phospholipid scramblase mRNA, a scramblase containing non-conservative substitutions, and by preventing posttranslational modifications such as fatty acylation. Also disclosed are methods to decrease the viability of metastatic or cancer cells by increasing the expression of phospholipid scramblase. Further

disclosed are methods for diagnosing cancers comprising quantitation of the levels of phospholipid scramblase in human patients (see page 73, claim 5 of Sims et al., 1999).

6. However, none of the above references disclose antisense compounds of 8 to 0 nucleobases in length targeting scramblase 3, or wherein said antisense oligonucleotides comprise the various modifications recited in the instant claims.

7. Phospholipid scramblase 3 (also known as PLSCR3, HuPLSCR3 and MuPLSCR3) was isolated as one of three new members of the phospholipid scramblase gene family (Wiedmer et al., Biochim. Biophys. Acta, 2000, 1467, 244-253). Upon identification of sequences in the EST database potentially encoding these three new phospholipid scramblase family members, a full-length cDNA encoding phospholipid scramblase 3 was obtained by PCR from a human erythroleukemia cell (HEL) cDNA library (Wiedmer et al., Biochim. Biophys. Acta, 2000, 1467, 244-253).

8. Branch teach that in order to maximize target site specificity the length of antisense oligonucleotides should be 17 base pairs or longer, since sequences of 17 base pairs or more would have a high probability of occurring only once in the haploid human genome. However, increasing the length of the oligonucleotide beyond this minimum would likely stabilize non-specific binding to mismatch sequences (p. 47, para. 5-6).

9. Monia et al. teach the design of antisense oligonucleotides comprising various modifications, including phosphorothioate modified internucleoside linkages (col. 8, line 41-43), 2'-O-methoxyethyl sugar modifications (col. 10, line5), 5-methylcytosine modified nucleobase (col. 10, line 31-32), and wherein the antisense oligonucleotide is a chimeric oligonucleotide (col. 11, line 51). The modified or substituted oligonucleotides of Monia et al. are preferred over

native (unmodified or unsubstituted) forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced binding to target and increased stability in the presence of nucleases (col. 8, lines 2-6). Additionally, Monia et al. teach the use compositions comprising antisense oligonucleotides and a pharmaceutically acceptable carrier or diluent, and further comprising a colloidal dispersion system in order to enhance the stability of oligonucleotides introduced into cells and to target oligonucleotides to a particular tissue or cell (col. 15, lines 19-41).

10. Agrawal provides motivation for designing antisense oligonucleotides targeting various regions of a target mRNA, including for example the coding region and the 5'-UTR and 3'-UTR of a target mRNA. According to Agrawal et al. "[I]t is considered preferable, therefore, to screen a number of oligonucleotides that encompass different regions on RNA to identify a set of optimal target sites, including the 5'- and 3'-untranslated regions (UTRs), initiation codon site, coding region and intron-exon junctions." (page 77, 1st para.) Additionally, Agrawal et al. generally states (regarding the feasibility of utilizing antisense technology), "antisense technology has become an essential laboratory tool to study and understand the function of any newly discovered genes in recent years."

11. It would have been obvious to one of ordinary skill in the art at the time of filing to modify the teachings of to produce the compounds and compositions according to the present invention. One of ordinary skill in the art would have been motivated to modify the teachings of Wiedmer and Sims (WO 97/37225 and WO 99/1935), and Sims et al. (WO 99/36536), in view of Wiedmer et al. (2000), Branch (1998), Monia et al. and Agrawal et al. to make the antisense compounds targeting phospholipid scramblase 3 according to the present invention. One of

ordinary skill in the art would have been motivated to design antisense compounds to comprise about 17 nucleobases in length or more, because antisense compounds of about 17 nucleobases in length would enhance target site specificity for the antisense to its target mRNA (Branch). One of ordinary skill in the art would have been motivated to further modify the antisense compounds of Wiedmer and Sims, and Sims et al. to comprise phosphorothioate modified internucleoside linkages, 2'-O-methoxyethyl sugar modifications, 5-methylcytosine modified nucleobases, or wherein said antisense compound is a chimeric compound, because according to Monia et al. these modifications would enhance the cellular properties of antisense compounds as compared to unmodified antisense compounds. Moreover, one of ordinary skill in the art would have been motivated to design compositions comprising the antisense compounds according to the present invention and a pharmaceutical carrier or diluent, and further comprising a colloidal dispersion system because Monia et al. teach that compositions designed according to this manner would enhance the stability of oligonucleotides introduced into cells and would help to target oligonucleotides to a particular tissue or cell.

12. Moreover, one of ordinary skill in the art seeking methods to extend the viability of mammalian cells by would have been motivated to design antisense oligonucleotides targeting phospholipid scramblase 3, since Sims et al. (1999) teach that inhibiting the expression of a phospholipid scramblase in mammalian cells increases the viability of these cells. Moreover, one of ordinary skill in the art seeking to further understand the role of phospholipid scramblase 3 in mammalian cells would have been motivated to design antisense oligonucleotides targeting the mRNA encoding the phospholipid scramblase 3 gene, since according to Agrawal, if the sequence of a gene is known, designing antisense oligonucleotides to target that gene would

allow the ordinary skilled artisan to further explore and understand the function of that particular gene.

13. Therefore, the invention as a whole is prima facie obvious over Wiedmer and Sims (WO 97/37225 and WO 99/1935), and Sims et al. (WO 99/36536), in view of Wiedmer et al. (2000), Branch (1998), Monia et al. and Agrawal et al.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on Monday-Thursday, 8:30 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE